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EXAMINER	
HOWARD, ZACHARY C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,018	GOLZ ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11,25 and 27-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-11,25 and 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/3/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 12/3/07 has been entered in full. Claims 1, 2, 3 and 25 are amended. Claim 5, 12-24 and 26 are canceled. New claims 27-30 are added.

In view of Applicants' cancellation of all claims directed to non-elected inventions (claims 12-24 and 26), the restriction requirement set forth previously is withdrawn. However, if new claims to non-elected inventions are introduced the restriction requirement will be reinstated.

Claims 1-4, 6-11, 25 and 27-30 are under consideration in the instant application.

Information Disclosure Statement

The Information Disclosure Statement of 12/3/07 has been considered.

Withdrawn Objections and/or Rejections

All rejections of claim 5 are moot in view of Applicants' cancellation of this claim.

The objections to claims 1-3 at pg 2 of the 9/4/07 Office Action are *withdrawn* in view of Applicants' amendments to the claims.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-11, 25 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention. This rejection was set forth at pg 3-12 of the 9/4/07 Office Action for claims 1-4, 6-11 and 25; new claims 27-30 are herewith added.

Applicants' arguments (12/3/07) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the specification teaches the association of NPFF2 with hematological diseases on pg 58 (lines 14-15) and supports this teaching with NPFF2 expression data from hematological tissues (Table 1) and that "NPFF2 polypeptide is highly expressed in tissues of the hematological system". Applicants point to Miller et al (1988) as teaching that elevation of intracellular calcium is a signal that mediates the effect of hematopoietic growth factors, which hematopoietic cells are dependent on for proliferation and differentiation.

Applicants' arguments have been fully considered but are not found persuasive. The teaching from page 313 of Miller quoted by Applicants fully reads "elevation in [Ca_c] is an intracellular signal that mediates the effect of these hematopoietic growth factors" (the underlined word was omitted from Applicants' quotation). It is clear that Miller is referring to the factors mentioned in the previous sentence, erythropoietin (EPO) and GM-CSF. It is well-known in the art that these growth factors operate through single transmembrane cytokine receptors that are not G-protein coupled receptors (see Richmond et al, 2005. TRENDS in Cell Biology. 15(3): 146-155). As noted by Richmond (see Abstract), the EPO receptor was discovered in 1989 (after the publication of Miller) and has been shown to be involved in the "EPO-dependent Ca2+ flux" in erythroid development (pg 151). Thus, the fact that NPFF2 is expressed in erythrocytes does not suggest that said GPCR has a role in the erythropoietin or GM-CSF-dependent proliferation and differentiation of hematopoietic cells. Therefore, it is maintained that based on the limited teachings of the specification and prior art, the skilled artisan would not be able to predict whether or not a modulator of an NPFF2-activity (such as alteration of intracellular calcium) could be used to treat a hematological disease. Neither the specification nor the prior art teach provide any reasonable correlation between NPFF2 activity and hematological diseases (either in a general or any species disease). The specification states, "NPFF2 is highly expressed in erythrocytes and other

tissues of the hematological system. The expression in the above mentioned tissues suggests an association between NPFF2 and hematological diseases. NPFF2 can be regulated in order to treat or to diagnosis hematological disorders" (pg 58, lines 13-16). However, the skilled artisan would recognize that gene expression in a particular tissue does not necessarily indicate that the encoded protein has a role in a disease associated with said tissue. A gene can be expressed in a tissue without having a role in a particular disease associated with that tissue. As shown by Applicants' working examples, NPFF2 is expressed in a wide variety of tissues, with the highest levels of expression in many tissues other than erythrocytes. It is possible that NPFF2 activity has a role in said tissues, including erythrocytes, that is entirely unrelated to any disease associated with said tissues. As set forth previously, Goh et al (2007; cited previously) demonstrate that hundreds of different genes are expressed reticulocytes (pg 175). The skilled artisan could not predict which, if any, of these expressed genes is associated with one or more hematological diseases. Even if a particular gene is found to have a role in erythropoiesis, the skilled artisan could not predict whether or not it would also have a role in a hematological disease, such that modulating its activity would treat said disease. As such, it is not predictable whether or not a modulator of NPFF2 calcium mobilization could be used to treat one or more hematological diseases. Furthermore, the specification provides no guidance as to whether an agonist or an antagonist of NPFF2 would provide the therapeutic treatment for a hematological disease. In order to use the claimed method to identify a therapeutic, the skilled artisan would need to first practice the claimed method to identify a modulator of the calcium mobilization of NPFF2, and then engage in further experimentation to test whether or not the modulator could be used to treat one or more hematological diseases.

Applicants further argue that claim 1 is "simply a screening method for compounds which bind to a human NPFF2 polypeptide" and "does not require identification of a test compound which binds to a human NPFF2 polypeptide as also able to alter NPFF2 activity".

Applicants' arguments have been fully considered but are not found persuasive. The claimed method is not "simply a screening method"; instead it is a screening

method that recites the intended use of identifying compounds that may be useful in treating a hematological disease. If an intended use is recited, it must meet the meet the requirements of 35 U.S.C. 112, first paragraph. Identification of a test compound that can bind to an NPFF2 polypeptide does not allow the skilled artisan to predict whether or not said binding partner can also alter an activity of the NPFF2 polypeptide. A test compound can bind to a receptor without altering its activity. The skilled artisan would still need to test said binding partner in an assay that measured the ability of the binding partner to modulate NPFF2 activity. The specification does not teach a use for binding agents that do not also modulate NPFF2 activity.

Applicants further argue that "it is well known that not all agents identified in a screening method will become therapeutics, and the claims do not require confirmation that a test compound identified as a modulator of the calcium mobilization produced by NPFF2 polypeptide can be used to treat a hematological disease".

Applicants' arguments have been fully considered but are not found persuasive. For the reasons set forth previously and reiterated herein, the specification does not enable use of the claimed methods to identify compounds for treatment of any hematological diseases. Applicants argue that screening methods do not require confirmation that any of the identified compounds be useful in treating hematological disease. However, the specification does not provide any guidance on using compounds that can modulate NPFF2 polypeptide activity other than in treating hematological disease. If the compounds are not useful in treating hematological diseases, then what are they useful for? It would require undue experimentation for the skilled artisan to investigate a use for the identified compounds other than in treating hematological disease.

Applicants further argue that working examples are not required to enable an invention and point to *In re Long* (1966) in support, and argue that "lack of a working example should not be given undue weight because the inventors have provided adequate direction for carrying out the claimed methods". Applicants further argue that the previous Office Action did not provide a reasonable basis to question the enablement of the claims.

Applicants' arguments have been fully considered but are not found persuasive. The lack of a working example was not given undue weight in the rejection set forth previously and maintained herein; instead, the presence or absence of working examples was merely one consideration included in the *Wands*-type analysis set forth in the rejection. It is maintained herein that said analysis provided a reasonable basis to question the enablement of the claims.

Furthermore, Applicants' response contains no arguments with respect to the following portion of the rejection set forth previously. Even if the claimed methods were enabled for a method of screening to identify a therapeutic using a polypeptide of SEQ ID NO: 2 (or residues 103-522 of SEQ ID NO: 2 as taught by Bonini), they would lack enablement for a method of screening using other variants of SEQ ID NO: 2 for the reasons set forth previously. Each of the amended claims encompasses use of a vast genus of variant "human NPFF2" polypeptides. As set forth previously, the specification teaches that an "NPFF2 polypeptide" includes not only a polypeptide of SEQ ID NO: 2 but also variants which show at least 80% homology to SEQ ID NO: 2, and wherein said polypeptide "has NPFF2 activity" (pg 9, lines 1-15). The polypeptide of SEQ ID NO: 2 consists of 522 amino acids; therefore, a variant with 80% homology has 104 amino acids that differ from SEQ ID NO: 2. The amendment to limit the claims to "human NPFF2" does not change the scope of the claims with respect to SEQ ID NO: 2, because SEQ ID NO: 2 is a human NPFF2 sequence. Prior art was cited teaching that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (Wells (1990); Ngo et al (1995); each cited previously). Prior art was also cited teaching that the art recognizes that function cannot be predicted from structure alone (Bork (2000); Skolnick et al (2000); Doerks (1998); Smith and Zhang (1997); Brenner (1999); Bork et al (1996); each cited previously). In view of the limited teachings of specification regarding the nature of active variants of SEQ ID NO: 2 and the teachings of the relevant art regarding the difficulty in predicting functional variants of a protein it would require undue experimentation to make and test (for "NPFF2 activity") each member of the vast genus of variants encompassed by the claims.

With respect to claims 1-4 and 6-11, it is noted that the portion of the enablement rejection directed to non-isolated host cells is moot in view of Applicant's amendments to independent claims 1, 2 and 3 that limit the contacting step of the methods to "in vitro". However, independent claim 25 still encompasses identifying a regulator of NPFF2 using *in vivo* methods of screening. The specification clearly contemplates transgenic animals with cells exogenously expressing the polypeptides of the invention (Example 14, pg 99-100). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with an NPFF2 gene is demonstrated to express the encoded peptide. The unpredictability of the art is very high with regards to making transgenic animals (Wang et al, 1999; Kaufman et al, 1999; each cited previously). It is maintained for the reasons set forth previously that due to the large quantity of experimentation necessary to generate a transgenic animal expressing the disclosed protein, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that establishes the unpredictability of making transgenic animals, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1-4, 6-11, 25 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth at pg 13-15 of the 9/4/07 Office Action for claims 1-4, 6-11 and 25; new claims 27-30 are herewith added to the rejection.

Applicants' arguments (12/3/07) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that independent claims 1-3 have been amended to limit NPFF2 polypeptides to human NPFF2 polypeptides, which Applicants argue was well known in the art before the priority date of the application. Applicants point to *Capon v. Eshhar* (2005) in support of the argument that "written description of a gene which is well known in the art does not require a structural recitation either in the specification or in the claims" and "a sequence identifier for a well-known protein such as NPFF2 should also not be required". Applicants argue that the skilled artisan would "readily recognize the genus of human NPFF2 polypeptides because these polypeptides were known in the art".

Applicants' arguments have been fully considered but are not found persuasive. The rejection set forth in previous Office Action did not require a sequence identifier for the NPFF2 polypeptide used in the claim methods, which as acknowledged in said Office Action, was known in the prior art. Instead, the rejection held that each of the claims is a genus claim that encompasses use of a genus of variant "NPFF2" polypeptides. As set forth previously, the specification teaches that an "NPFF2 polypeptide" includes not only a polypeptide of SEQ ID NO: 2 but also variants which show at least 80% homology to SEQ ID NO: 2, and wherein said polypeptide "has NPFF2 activity" (pg 9, lines 1-15). The polypeptide of SEQ ID NO: 2 consists of 522 amino acids; therefore, a variant with 80% homology has 104 amino acids that differ from SEQ ID NO: 2. The amendment to limit the claims to "human NPFF2" does not change the scope of the claims with respect to SEQ ID NO: 2, because SEQ ID NO: 2 is a human NPFF2 sequence. The instant specification fails to describe the entire genus of variant human NPFF2 polypeptides that will function in the claimed methods (i.e., which mutations of the prior art sequence will retain an "NPFF2 activity"). Therefore it is maintained for the reasons set forth in the 9/4/07 Office Action that only methods of screening comprising use of a polypeptide of SEQ ID NO: 2 (or residues 103-552 of SEQ ID NO: 2 as taught by the prior art), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Cikos et al, 1999. Biochemical and Biophysical Research Communications. 256: 352-356; cited previously. This rejection was set forth at pg 16-17 of the 9/4/07 Office Action.

The rejection is first restated in view of Applicants' amendments to the claims and then Applicants' arguments are addressed.

Applicants have amended the preamble of claim 1 to recite "A method of screening for agents that may be useful in the treatment of hematological disease in a human". As such, the preamble of the claim is now limited to the elected species of disease under consideration ("hematological diseases"). The amended preamble is still interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed method over one from the prior art. See MPEP 2111.02, "Effect of Preamble", section II, "Preamble Statements Reciting Purpose or Intended Use". As such, the method of claim 1 encompasses a method comprising the recited method steps.

As described previously, Cikos et al (1999) teach a NPGPR polypeptide that is 100% identical to the NPFF2 polypeptide (SEQ ID NO: 2) disclosed by the instant application (an alignment of the two sequences is attached to this Office Action as Sequence Alignment #1). Cikos et al further teach, "[p]reliminary binding studies with transfected CHO cells indicate that [I^{125}] peptide YY (a NPY receptor ligand) does not bind to NPGPR" (pg 356). As such, Cikos et al teach a method of contacting a test compound (YY) with a NPFF2 polypeptide (NPGPR) and detecting binding of said test compound to said NPFF2 polypeptide (in this study, no binding of the test compound was detected). The teachings of Cikos meet all of the limitations of the method steps of amended claim 1 for the following reasons.

Step (i) of claim 1 has been amended to limit the contacting performed to *in vitro* and with a human NPFF2 polypeptide. Instant SEQ ID NO: 2 is disclosed as a human

sequence; therefore, the identical sequence disclosed by Cikos is inherently a human NPFF2 polypeptide. Furthermore, the contacting step of Cikos was performed in vitro with transfected CHO cells (pg 356). Therefore, the teachings of Cikos meet the limitations of step (i) of amended claim 1.

Step (ii) of claim 1 has not been amended. As set forth previously, the term "detecting binding" in step (ii) is still broadly interpreted to encompass a "detection" step (i.e., detecting whether or not binding has occurred).

New step (iii) has been added that recites "identifying a test compound that binds to said NPFF2 as agent that may be useful in the treatment of a hematological disease". However, the teachings of Cikos meet this limitation for the following reasons. Step (iii) is a mental identification that applies only to a compound that binds and does not result in a physical manipulation of the binding compound; thus the new step does not render the claimed method as patentability distinct from the method taught by Cikos. Furthermore, the new step only requires that the agent may be useful to treat hematological disease; the converse of "may" is "may not"; thus, this recitation inherently applies to all binding compounds because they all "may" or "may not" be useful in the recited manner. The method of Cikos teaches screening for test compounds that bind; any compound so identified inherently may (or may not) be useful in the recited treatment.

Claim 4 depends from claim 1 and limits the contacting step to "in or at the surface of a cell". As described above, Cikos et al perform the binding assay with NPGPR expressed in CHO cells. Furthermore, NPGPR is a cell membrane expressed GPCR; therefore, the contacting step occurs at the cell surface. As such, the teachings of Cikos et al described above also anticipate claim 4.

Claim 8 depends from claim 1 and limits the compound to a compound coupled to a detectable label. As described above, the test compound used by Cikos et al is coupled to a detectable [I^{125}] label. As such, the teachings of Cikos et al described above also anticipate claim 8.

Applicants' arguments (12/3/07; pg 6-7) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that Cikos does not meet the standards set forth in *Verdegaal Bros v. Union Oil of California* (1987) or *Richardson v. Suzuki Motor Co* (1989). Applicants point to the amendments to claim 1 and argue that Cikos does not teach any association with human NPFF2 with hematological disease.

Applicants' arguments have been fully considered but are not found persuasive. The Examiner does not dispute the standards set forth in *Verdegaal* or *Richardson*. The rejection meets these standards for the reasons set forth above in view of the amended claims. Cikos teaches, in as complete detail, each and every element of an identical invention as set forth in the claims. Furthermore, for the reasons set forth above, Cikos does not need to specifically teach an association with human NPFF2 and hematological disease; the recitations in the claims that refer to such an association are either intended uses or inherent features of binding compounds.

Claims 1-4, 6-11, 28 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonini et al, 2000. Journal of Biological Chemistry. 275(50): 39324-39331; cited previously. This rejection was set forth at pg 17-20 of the 9/4/07 Office Action for claims 1-4 and 6-11; new claims 28 and 30 are herewith added.

The rejection is first restated in view of Applicants' amendments to the claims and then Applicants' arguments are addressed.

Applicants have amended the preamble of claim 1 to recite "A method of screening for agents that may be useful in the treatment of hematological disease in a human". As such, the preamble of the claim is now limited to the elected species of disease under consideration ("hematological diseases"). The amended preamble is still interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed method over one from the prior art. See MPEP 2111.02, "Effect of Preamble", section II, "Preamble Statements Reciting Purpose or Intended Use". As such, the method of claim 1 encompasses a method comprising the recited method steps.

As described previously, Bonini et al (2000) teach a NPFF2 polypeptide that is 100% identical to residues 103-522 of SEQ ID NO: 2 (see pg 2 of Sequence Alignment #1 wherein isoform #2 is noted to be missing residues 1-102). Bonini et al discuss the

difference between this isoform and the isoform identified earlier by Cikos et al (described above and identical to instant SEQ ID NO: 2): "NPGPR is nearly identical to NPFF2 except that the N terminus of NPGPR is longer by 102 amino acids" (pg 39326). Bonini et al further teach, "Membranes from transiently transfected COS-7 cells exhibited high affinity, saturable [I^{125}]1DMeNPFF binding for both NPFF1 and NPFF2" (pg 39327). As such, Bonini et al teach a method of contacting a test compound ([I^{125}]1DMeNPFF) with a NPFF2 polypeptide and detecting binding of said test compound to said NPFF2 polypeptide. The teachings of Bonini meet all of the limitations of the method steps of amended claim 1 for the following reasons.

Step (i) of claim 1 has been amended to limit the contacting performed to *in vitro* and with a human NPFF2 polypeptide. The NPGPR sequence taught by Bonini referred to above is a human sequence (see pg 39326 and Figure 3). Furthermore, the binding assay taught by Bonini was performed in vitro using membranes from transfected COS-7 cells (see above). Therefore, the teachings of Bonini meet the limitations of step (i) of amended claim 1.

Step (ii) of claim 1 has not been amended. As set forth previously, the term "detecting binding" in step (ii) is still broadly interpreted to encompass a "detection" step (i.e., detecting whether or not binding has occurred).

New step (iii) has been added that recites "identifying a test compound that binds to said NPFF2 as agent that may be useful in the treatment of a hematological disease". However, the teachings of Bonini meet this limitation for the following reasons. Step (iii) is a mental identification that only applies to a binding compound and does not result in a physical manipulation of the binding compound; thus the new step does not render the claimed method as patentability distinct from the method taught by Bonini. Furthermore, the new step only requires that the agent may be useful to treat hematological disease; the converse of "may" is "may not"; thus, this recitation inherently applies to all binding compounds because they all "may" or "may not" be useful in the recited manner. The method of Bonini teaches screening for test compounds that bind; any compound so identified inherently may (or may not) be useful in the recited treatment.

The method of amended claim 2 encompasses a method of screening comprising determining the activity of a human NPFF2 polypeptide a certain concentration of a test compound or in the absence of said test compound, and determining the activity of said polypeptide at a different concentration of said test compound, and identifying the test compound as a potential therapeutic agent useful in the treatment of a hematological agent if the activity of the NPFF2 polypeptide is different, and wherein the activity of the polypeptide results in an alteration of intracellular calcium. Bonini et al further teach, "[c]o-transfection of rat NPFF1 or human NPFF2 receptors with either $G\alpha_{q/i3}$ or $G\alpha_{q/z5}$ led, in both cases, to the activation of NPFF of intracellular Ca^{2+} mobilization in a concentration-dependent manner (Fig. 5)" (pg 39327). As indicated, Figure 5B shows a comparison of the activity of NPFF2 at various concentrations of the test compound NPFF. Step (iii) of claim 2 recites that any test compound that can alter activity is identified as a "potential therapeutic". However, the teachings of Bonini meet this limitation for the following reasons. Step (iii) is a mental identification that only applies to an activity-altering compound and does not result in a physical manipulation of the binding compound; thus the new step does not render the claimed method as patentability distinct from the method taught by Bonini. Furthermore, the new step only requires that the agent is a potential therapeutic useful in treatment of hematological disease; thus, this recitation inherently applies to all activity-altering compounds because they all are potentially useful in the recited manner. The method of Bonini teaches screening for test compounds that alter activity; any compound so identified inherently potentially could be used in the recited treatment. As such, Bonini et al teach a method that anticipates instant claim 2.

The method of amended claim 3 encompasses a method of screening comprising determining the activity of a human NPFF2 polypeptide at a certain concentration of a test compound, determining the activity of said NPFF2 polypeptide at the presence of a compound known to be a regulator of a NPFF2 polypeptide, and identifying the test compound as a potential therapeutic agent useful in the treatment of a hematological agent if the activity of the NPFF2 polypeptide is different, and wherein the activity of the polypeptide results in an alteration of intracellular calcium. Table II of

Bonini et al demonstrates the activity of two compounds (FPP and PQRF-amide) in comparison to NPFF in activation of intracellular calcium mobilization. Each compound acts as an agonist of the NPFF2 receptor with a higher EC_{50} and lower response than NPFF. Therefore, Bonini teaches a method comprising determining the activity of NPFF2 polypeptide at a certain concentration of a test compound (FPP or PQRF-amide) and determining the activity of said NPFF2 polypeptide at the presence of a compound known to be regulator of a NPFF2 polypeptide (NPFF, known to be a regulator of NPFF2 in view of the results of Figure 5). As with claim 2, new method step (iii) is an inherent feature of the teachings of Bonini. As such, Bonini et al teach a method that anticipates instant claim 3.

Claim 4 depends from claim 1 and limits the contacting step to "in or at the surface of a cell". Bonini further teaches binding assays using the NPFF2 receptor expressed in HEK-293 cells (pg 38327). The NPFF2 receptor is a cell membrane expressed GPCR; therefore, the contacting step occurs at the cell surface. As such, the teachings of Bonini et al also anticipate claim 4.

Claim 6 depends from claim 1 and limits the method to one wherein "the step of contacting is in a cell-free system". As described above, Bonini et al teach binding assays using membranes from COS-7 cells. Isolated cell membranes meet the definition of a "cell-free system". As such, the teachings of Bonini et al described above also anticipate claim 6.

Claim 7 depends from claim 1 and limits the method to one wherein "the polypeptide is coupled to a detectable label". The phrase "coupled" broadly encompasses any form of binding, and the phrase "detectable label" encompasses a radiolabeled ligand. As such, the binding assays described by Bonini et al, wherein a radiolabeled ligand binds to the NPFF2 receptor, meet the definition of a coupling to a detectable label. As such, the teachings of Bonini et al described above also anticipate claim 7.

Claim 8 depends from claim 1 and limits the compound to a compound coupled to a detectable label. As described above, the NPFF test compound used by Bonini et al

is coupled to a detectable [I^{125}] label. As such, the teachings of Bonini et al described above also anticipate claim 8.

Claim 9 depends from claim 1 and limits the method to one wherein, "the test compound displaces a ligand which is first bound to the polypeptide". Bonini further teaches, competition binding assays wherein several ligands are test for the ability to displace the ligand [I^{125}]1DMeNPFF (see Table I on pg 39328). As such, the teachings of Bonini et al described above also anticipate claim 9.

Claims 10 and 11 each depend from claim 1 and respectively limit the method to one wherein, "the polypeptide is attached to a solid support" (claim 10) or "the compound is attached to solid support". The claims do not limit the step at which the polypeptide is attached to a solid support; therefore, the claim broadly encompasses a method wherein the polypeptide or compound is attached to a solid support after incubation with the ligand. Furthermore, the claims encompass direct or indirect (e.g., via another compound) attachment. The membrane binding assays conducted by Bonini et al result in both the membrane-bound receptor and ligand being deposited on a "double layer of glass fiber filters", which are used for scintillation counting to measure the quantity of radiolabeled ligand that bound to the receptor. Glass fiber filters meet the definition of a solid support. Therefore, Bonini et al teach a binding assay which results in the NPFF2 polypeptide and the radiolabeled NPFF ligand each being attached to a solid support. As such, the teachings of Bonini et al described above also anticipate each of claims 10 and 11.

New claims 28 and 30 depend from claims 2 or 3 (respectively) and each limit the method of the parent claim to one wherein the polypeptide (NPFF2) is coupled to a detectable label. In the teachings of Bonini described above with respect to claims 2 or 3, the NPFF2 polypeptide is coupled to a ligand (NPFF, FPP or PQRF-amide), each of which is a detectable label.

New rejections necessitated by Applicants' amendment

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

Claims 27 and 29 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

New claims 27 and 29 depend from claims 2 or 3 (respectively) and each recite "wherein the step of contacting is in a cell-free system". However, each parent claim (2 or 3) has been amended to by limited to a method of screening by determining the activity of an NPFF2 polypeptide, "wherein the activity of the polypeptide results in an alteration of intracellular calcium". Thus, dependent claims 27 and 29 are limited to methods of screening wherein intracellular calcium (i.e., calcium inside a cell) is measured in a cell-free system (i.e., a system without cells and therefore without an "intracellular" locale). At pg 1 of the 12/3/07 response, Applicants indicate that support for new claims 27-30 can be found in claims 4 and 6 as originally filed. However, while original claim 6 was directed to assay in a cell-free system, and depended from claims 2 and 3, original claims 2 and 3 did not comprise an activity that is alteration of intracellular calcium. The entire specification has been reviewed and no support for new claims 27 or 29 has been found. The specification discusses assays wherein intracellular activity is measured; however, these assays are all described as being cell-based rather that cell-free (see ¶ [0171] of the published application). The specification discusses cell-free assays; however, none of these assays is described as involving alteration of intracellular calcium (see ¶ [0172] of the published application). Nowhere does the specification describe an assay with the specific combination of cell-free assay and an activity of alteration of intracellular calcium, nor does the concept of the specific assay flow naturally from the disclosure of the specification. Therefore, the specification as originally filed lacks support for the method encompassed by new claims 27 and 29.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646